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13 ABSTRACT

In 1979-80 we collected and re-examined all breast biopsies performed in Israel by a single pathologist (Dr. M. Black) in New York, using his prognostic grading system, nuclear differentiation and Lymphocyte Reticular Endotelial (LRE) response for benign breast diseases (BBD). The complete cohort consisted of about 3500 women. By September 1995, 460 women were traced and 349 of them were interviewed. Preliminary data show that about 42% of these women went through a second biopsy and 22% went through >2 biopsies. The latter pathological slides were sent to Dr. Black in the U.S. for re-evaluation. First follow-up for morbidity and mortality was done by linkage of our file with that of the Cancer Registry 2.2% of women with normotypic (grade 1), 3.3% of hyperplastic (grade 2), and 9% of atypic, precancerous mastopathy (grade 3-4) developed breast cancer (BC). Mortality of the cancer patients in the cohort was 38% for in-situ BC and for 67.2% invasive BC. A second stage of this study i.e. a nested case control study of the BBD cohort, using a questionnaire with complete hormonal and parity history as well as personal and family history as well as personal and family history of benign and malignant BC, physical activity and alcohol drinking habits, is on the way.

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STUDY PURPOSE

Background

This study offers a unique opportunity to evaluate the course of development of the whole range of benign and malignant breast diseases diagnosed in a national incidence study conducted fifteen years ago, in relation to a histologic type and selected risk factors, in women belonging to distinct ethnic groups who also differ in their BC incidence.

In Black's BBD prognostic system the essential feature of Black-Chabon grading system is based on a score of 1 to 5 describing a degree of ductal atypia. Normotypic lesions included those classifed as normoplastic (Grade 1) and hyperplastic (Grade 2). The normoplastic lesions included those conventionally categorized as cystic changes, stromal fibrosis, duct ectasia, and normal-appearing breast parenchyma. The hyperplastic lesions included those conventionally classified as intraductal papillomas, papillomatosis, adenosis, and duct hyperplasia without atypia. The term benign proliferative mastopathy was ascribed to the preceding group of conditions with duct Grades 1 to 4. Minimal, moderate and marked degrees of ductal and/or lobular atypia were graded as 3-5, respectively. A grading of 5 essentially coincides with the traditional category of Ca *in situ*, while Grades 3 and 4 are sometimes diagnoses as Ca *in situ.*

The evolution of BC from normal tissue to malignancy has a long natural history which may be a multistage process that proceeds through duct cell hyperproliferation to atypia, *in situ* growth, and malignant transformation. This tumorogenesis model may be associated with several genetic, hormonal and

reproductive factors that may act to depress, or enhance, the final outcome in this dynamic continuum.

The Israeli National Population Registry maintains a registry of all citizens and permanent residents in Israel. The registry includes first and second names; father's first name, I.D. number; sex; date of birth; country of origin; year of immigration; marital status; address; vital status; and date, place and cause of death, where applicable. Each Israeli citizen and each permanent resident, has a unique nine-digit National I.D. number which cannot be assigned to anyone else. This number is used for many purposes and facilitates record linkage. The Israel National Population Registry is updated on a routine basis for births, deaths, and in- and out-migration, and is corrected by linkage with census data.

Israeli population is characterized by its marked ethnic diversity and varying incidence of BC risk which parallels racial black/white differences in the U.S. Follow-up for morbidity and mortality can easily be done due to the possibility of linkage of the original epidemiological data with the Cancer Registry using a unique I.D. number, identifying all Israel citizens.

Our study will allow identification of factors (reproductive, hormonal, family history, etc.) affecting BC onset. The temporal influence of these recognized risk factors associated with breast events will be investigated in a gradient of pathological subgroups (normotypic, hyperplastic, atypic, in situ) and BC incidence.

The study is based on a fifteen-year follow-up of the cohort of 3500 women diagnosed nationwide for benign and malignant breast lesions, between July 1979 and June 1980. A particular feature of the study population is that it stems from a single community but comprises subgroups with varying BC incidence; high risk women born in Europe, America and Israel, and low risk women originating from the

Middle East and North Africa. The age-adjusted incidence rates of these groups in the late 1980's were 87.0 and 57.2 per 100,000 respectively, a gradient similar to the one observed between US whites and blacks.

Significance

This study offers a unique opportunity to evaluate the progression of benign and malignant breast disease on a whole community base population.

Results will contribute to shedding light in respect to the role of BBD in general and its specific histologic types in BC causation, taking into account interactions with main hormonal and demographic risk factors.

TECHNICAL OBJECTIVES

The specific aims are:

1. To assess morbidity patterns in a nationwide cohort of women with breast lesions by histopathological type and by ethnic origin.
2. To compare the prognostic value of Black-Chabon atypia-based grading system of BBD to the "traditional" histopathologic diagnosis, as predictors for progression from benign to malignant breast lesions.
3. To evaluate the prognostic significance of selected specific characteristics of breast neoplasms by clinical stage (TNM): histopathology; laterality of sequential neoplastic events; angiogenesis; degree of nuclear differentiation of the tumor cells (expressed as nuclear grade (NG)); and cell mediated immunity to autologous cancer cells (as manifested by microscopically demonstrable lymphoreticuloendothelial (LRE) response).
4. To evaluate the role of selected hormonal and other factors, on the course of progression from benign to malignant breast lesions.

5. To assess the role of demographic and medical characteristics on the development of a second BC.

6. To establish a national datafile for subsequent long-term follow-up of this population.

Questionnaire

All patients are interviewed in their homes by means of a standard structured questionnaire in Hebrew containing items on the following list of subjects.

Demographic information:
Name, birth date, marital status, year of immigration, country of origin, education, profession, working place, working exposure.

Smoking history; Drinking habits; Weight: adult life (now; age 18); Height.

Menstrual history: Reproductive history, parity
Hormone intake: OC

Sterility treatment and other:
Medical history: surgery, genitary tract morbidity
Radiation treatment

Diagnostic x-ray:
Mammographies in particular

Drugs taken for at least three consecutive months

Family history of breast cancer; breast diseases; genitary cancer; other cancers

Physical activity; No. of active hours versus passive daily hours

WORK PROGRESS AND PRELIMINARY RESULTS

There was a late start of the study due to a delay in transfer of funds. Consequently the actual study months do not correspond to the original work flow.

Table 1 presents the study cohort by main diagnosis, representing all women going through breast biopsy in Israel during one year period (6.1.79 - 7.1.80) (Appendix), and identified 15 years later. The source of the demographic information

collected at time of first identification of cases consisted of the pathological records, which in many cases were found to be incomplete. During the last year completion of demographic information was done by tracing and identifying medical records in all hospitals in Israel. Our file was then linked to the Population Registry to further update addresses and vital status (complete name and address, year of birth, father's name and place of birth) to validate identification. As can be observed, 229 cases (8.4%) were not identified and we continue the tracing process individually. Unidentified women were found not to belong to one specific type of benign breast disease but are rather distributed similarly among the various diagnostic categories (9.5 in precancerous breast diseases and 9% in the normotypic benign breast disease and 8.3 in the invasive carcinoma patients).

Biological relationships between invasive breast carcinoma and non-invasive lesions have been obscured by the tendency to categorize most benign parenchymal lesions (excluding fibroadenoma) as fibrocystic disease, in spite of distinct differences in their proliferative and atypical characteristics.

Dissatisfaction with the prognostic value of traditional pathological categorization of BBD has led to the development characterization of BBD based on proliferation and atypical degree of changes of defined segments of the mammary duct system.

Table 2 shows results of 12 years BC morbidity follow-up. The prognostic value of Black-Chabon grading system of benign breast diseases was confirmed in findings in our cohort. An increased risk for breast cancer with increased grading was observed: from 2.2% in the normotypic normoplastic type of BBD (grade 1) to 9.0% in atypic precancerous mastopathy (grade 3).

We evaluated the frequency of subsequent BBD in a subgroup of 250 BBD women interviewed (table 3) and found that 64% of the women went through at least one additional biopsy , 42% had two biopsies, while 22% had three or more. All pathological slides of these biopsies are being reassessed by Dr. Black and the BBD history status by highest grade through life will be rechecked against BC morbidity in further follow-ups, before the end of the study period.

Table 4 shows the interview status of the nested case control study. By 1.6.95 we completed 349 interviews and a similar number is in process in the field. Response was 77.5%. Non response was mostly due to incorrect address and therefore should not be considered final. Non response by type of diagnosis shows a similar distribution among all types of diseases.

DISCUSSION

As can be observed from Table 2, 9% of BBD graded 3-4, developed breast cancer as compared to 2.2% in grade 1 BBD (normotypic normoplastic) while grade 2 has an in-between risk (3.3%). Using conventional diagnostic nomenclature fibrocystic BBD grade 2-3-4 would have just distributed among fibrocystic diseases.

Future plans

Breast cancer cohort - Follow-up of BC patients includes abstracting medical information from the oncological records in all hospitals in Israel. About 50% of these were identified. During the next year completion of BC follow-up will be done, and a special effort will be made to identify records on the basis of a personal, nationwide search.

Nested case control study - Interviews will be completed, and on line data entering will continue. A double check of case identification will be done by going back to unidentified cases by a second interviewer and, if needed, a special professional

tracer will be employed. Data analysis of familial BC and familial BBD is being considered for the next year.

Direct and inferential evidence indicates that the precursor to invasive progession is impeded by cell-mediated immunity to a particular immunogen that is characteristically expressed in the preinvasive phase of mammary carcinogenesis.

Evaluation of this component, LRE, response to the tumor was made in our cohort and will also be analyzed as marker for further BC morbidity. Within grade 2 and 3 there are many cases (67%) that were designed traditionally as fibrocystic disease.

Shipping of all pathological slides to N.Y will start next year. Dr. Black's visit to Israel is due November for special counselling and review of original pathological slides.

Table 1

Study cohort by main Black's diagnostic category

and current status

Diagnostic Category (1979-80)	Total Cohort (1979-80) n	Total Cohort Identified* (1995) n
Total BBD	2728**	2499
Normotypic/ hyperplastic (Grade 1-2)	2521	2303
Atypic, precancerous (Grade 3-4)	132	126
In situ (Grade 5)	75	70
Invasive	992	828

* *By Population Registry only (not home identification) for mortality and demographic information only (does not include non-responders)*

** *For about 10% of cases no review was done by Dr. Black, the complete cohort includes these women as well, with their histopathology by local pathologist*

PRELIMINARY DATA

Table 2

Number and percent of breast cancer (BC) in the BBD cohort, diagnosed by Black, and BC morbidity after 12 years of follow-up by category

Type of disease BBD (1979-80)	Total No. in the cohort*	BC (year 1991)	
	n	n	%
Normotypic-Normoplastic (Grade 1)	991	22	2.2
Normotypic-Hyperplastic (Grade 2)	932	32	3.3
Atypic precancerous mastopathy (Grade 3-4)	132	12	9.1
In situ Ca. (Grade 5)	62	3	4.8
Total	2117	79	3.1

* *total includes only women for whom all demographic characteristics were ascertained and were diagnosed originally by Dr. Black*

PRELIMINARY DATA

Table 3

BBD COHORT SUBSAMPLE
(n=250 interviews)

Frequency distribution of repeated breast biopsies

No. of Breast Biopsies	Total n	%
1	90*	36
2	105	42
3	36	14.4
≥4	19	7.6
Total	250	100

** no additional biopsy*

Table 4

Distribution of population by interview status and cause of non-response

					Non-response					
Total cohort	Interviewed		In process*		Refused		Not identified		Other reasons	
	n	%	n	%	n	%	n	%	n	%
2400	349	77.6	450	100	27	6	39	8.7	35	7.8

* *traced population of the nested case-control study until 8.1.95*